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(71) Applicant: Morgan, Lee Roy
725 Topaz Street
New Orleans Louisiana 70124(US)

(72) Inventor: Morgan, Lee Roy
725 Topaz Street
New Orleans Louisiana 70124(US)

(74) Representative: Brown, John David et al
FORRESTER & BOEHMERT
Widenmayerstrasse 4/I
D-8000 München 22(DE)

(54) Method and compounds for reducing dermal inflammations.

(57) Dermal inflammations which are induced and propagated by leukotrienes are treated by topically applying to the inflamed dermis the following compound:

$$R^3-S-(CH_2)_n-\underset{\displaystyle Y}{CH}-(CH_2)_p-X$$

wherein R^3 is H or thiol; n is 1-12; p is 0-12; X is a substituted carbonyl; and Y is aliphatic or branched hydrocarbon, aromatic, carbonyl, or substituted amide.

EP 0 300 100 A1

METHOD AND COMPOUNDS FOR REDUCING DERMAL INFLAMMATIONS

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to the treatment of indolent dermal irritations. More specifically, it concerns treatment of the persistent inflammations such as chemical ulcers, herpes ulcers, radiation burns, psoriasis and sunburn.

2. General Background of the Invention

Herpes ulcers, radiation burns, psoriasis and some chemical ulcers are indolent inflammations for which medical treatment has been unavailable or inadequate. Each of these conditions produces dermal eruptions and ulcers which persist painfully, sometimes for many months.

Herpes Infections

Infections caused by the herpes simplex virus produce eruption of one or more groups of vesicles or sores on the human body. Such eruptions characteristically occur on the vermillion border of the lips, at the external nares, on the glans, prepuce or vulva.

Herpes simplex virus type 1 is known as the "skin" or "above the umbilicus" virus and type 2 is known as the "genital" or "below the umbilicus" virus. The types cannot be distinguished in a culture, but can be distinguished on the basis of antibodies generated upon exposure to the virus. The two types cross react with one another in the laboratory and are, thus, very closely related to each other.

Herpes infections are commonly recrudescent and reappear during febrile illness or even physiological states such as menstruation and high stress.

Some herpes lesions, particularly those produced by herpes zoster, develop eruptive lesions in a linear pattern along dermal distributions of nerves on the face, trunk, abdomen, and extremities to produce extremely painful, eruptive, weeping lesions that heal extremely slowly with paraphesia. This type of infection is known as shingles and is seen in individuals with cancer or opportunistic debilitating infections that depress the immune system of the patient.

Various treatments for herpes hominis simplex have been proposed. Asculai, U.S. Pat. No. 4,147,803, reports that certain sorbitan derivatives have antiherpetic activity. DeLong et al. (U.S. Pat. No. 3,639,612) describes such activity for certain chalcogen containing heterocyclic compounds. Stedman (U.S. Pat. No. 3,555,355) discloses that certain cycloalkylamines have activity against herpes simplex as does cycloheximide (U.S. Pat. No. 4,427,684). Fleming et al. (U.S. Pat. No. 3,829,578) teaches that certain bis-basic ethers and xanthen-9-ones have anti-viral activity and Soichet (U.S. Pat. No. 4,312,884) describes such antiviral activity by Spectinomycin.

Kaufman et al., (Arch. Ophthalmol., 68:235-239 (1962)) reported treatment of herpes simplex keratitis with 5-iodo-2-deoxyridine (IUD). Schabel describes treatment of genital herpetic infection with 9-beta-D-arabino-fluranosyl adenine (Chemotherapy, 13:321-338 (1968)), and reported antiviral activity of 5-trifluoromethyl-2-deoxyuridine (N.Y. Acad. Aci., 130: 168-180 (1965)). Adams et al. (J. Infect. Dis., 133 (suppl) 151-159 (1976)) treated genital herpes infections with topical application of adenine arabinoside. Felber et al. (JAMA, 223:289-292 (1973)) describes treatment of herpes infections by application of a vital dye as neutral red or proflavine followed by exposure to light. Cheseman et al. (N. Eng. J. Med., 300:1345-1349 (1979)) and Pazin et al. (N. Engl. J. Med., 301: 225-230 (1979)) report the treatment of herpes simplex infection by human leukocyte interferon. Blough and Giuntioli (JAMA, 241:2798-2801 (1979)) described treatment of human genital herpes infections with 2-deoxy-D-glucose. Schaeffer et al. (Nature, 272: 583-585 (1978)), Fyfe et al. (J. Biol. Chem., 253:8721-8727 (1978)), Sely et al. (Lancet, 2:1257-1270 (1979)), Park et al. (J. Infect. Dis., 140:802-806 (1979)), and Pavan-Langston et al. (Am J. Ophthalmol., 86:618-623 (1978)) reported treatment of herpes infections by 9-(2-hydroxyethoxymethyl) guanine (Acyclovir). Fisher (Cutis,

29:467-472 (1982)) described treatment of herpes simplex infections with Amantadine Hydrochloride.

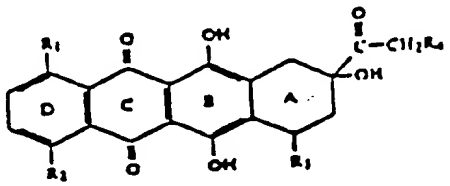
Other forms of treatment of herpes hominis simplex Type I and II include a variety of agents such as lysine, ascorbic acid, topical ether and topical chloroform, thymol, nonionic surfactants (U.S. Pat. Nos. 4,147,803 and 4,185,097) inactivated herpes viruses, zinc, urea, tannic acid (U.S. Pat. No. 4,285,934), glutaraldehyde, cow pox vaccine, intradermal injections of gamma globulins, and a surgical treatment by epidermal excisions of the herpetic lesions.

A mixture of L-lysine, gibberellic acid and urea has been reported to be useful in the treatment of H. simplex (U.S. Pat. No. 4,424,232). Similarly, transfer factor has been reported to be useful (U.S. Pat. No. 4,435,384). Adenosine monophosphate has also been reported to reduce pain and increase healing of herpes zoster lesions (JAMA).

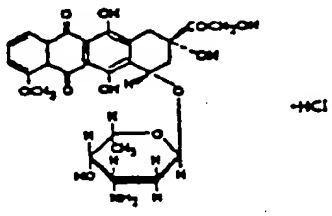
Chemical Ulcers

Another persistent, painful type of dermal inflammation is caused by accidental soft tissue extravasations from intravenous administration of anthracyclines such as doxorubicin (DOX).

The anthracyclines have the general formula:



and their essential structure is based on the anthraquinone ring which characteristically has a quinone functionality on the C ring and a hydroquinone function of the B ring. In addition, a hexose sugar is commonly attached through a glycosidic linkage at R^3. Daunosamine is the most common sugar to be found at R^3, R^1, and R^2, while R^4 can vary widely. The two anthracyclines presently in clinical use are doxorubicin (marketed by Adria Laboratories of Dublin, Ohio as ADRIAMYCIN) and duanomycin. In doxorubicin, R_1, R^2, and R^4 are H, OCH_3, and OH; this structure is shown below:



For duanomycin; R^1, R^2 and R^4 are H, OCH_3 and H, respectively, while R^3 is daunosamine.

The anthracyclines are members of the Rhodomycin group of antibiotics produced by Streptomyces, they have considerably activity against a wide range of human and animal tumors. Two members of this group, daunomycin and doxorubicin (DOX), are widely used as anticancer agents. However, the clinical usefulness of these drugs is impaired because they cause cardiac damage in both man and animals when administered systemically.

Another serious toxicity associated with these agents is tissue necrosis cause by extravasation into subcutaneous tissue during intravenous administration. This problem is very harmful and painful because chemical ulcers induced by anthracyclines tend to last many months and usually require surgical debridement before subsiding.

A number of agents have been injected or topically applied to treat doxorubicin (DOX) skin necrosis. Sodium bicarbonate (Lancet, 2:417 (1978)), alpha tocopherol, beta adrengics, diphenlydramine and cimetidine (Cancer Treat Res., 65:1001 (1981)), DMSO (Cancer Treat Rep., 67:407 (1983)) and corticosteroids (Am. J. Nurs., 79:94 (1979)) have all been used, but none of them have been widely accepted.

N-acetylcysteine is an agent that has been extensively evaluated for all types of DOX toxicities. Previous reports have indicated, however, that DOX ulcers became worse when NAC was injected

intradermally proximal to the ulcers in mice. (Cancer Treat. Rep., 65:1001 (1981)). With the exception of corticosteroids, surgical debridement and graft placement, no satisfactory par nteral or topical formulation has been available for treating anthracycline induced ulcers.

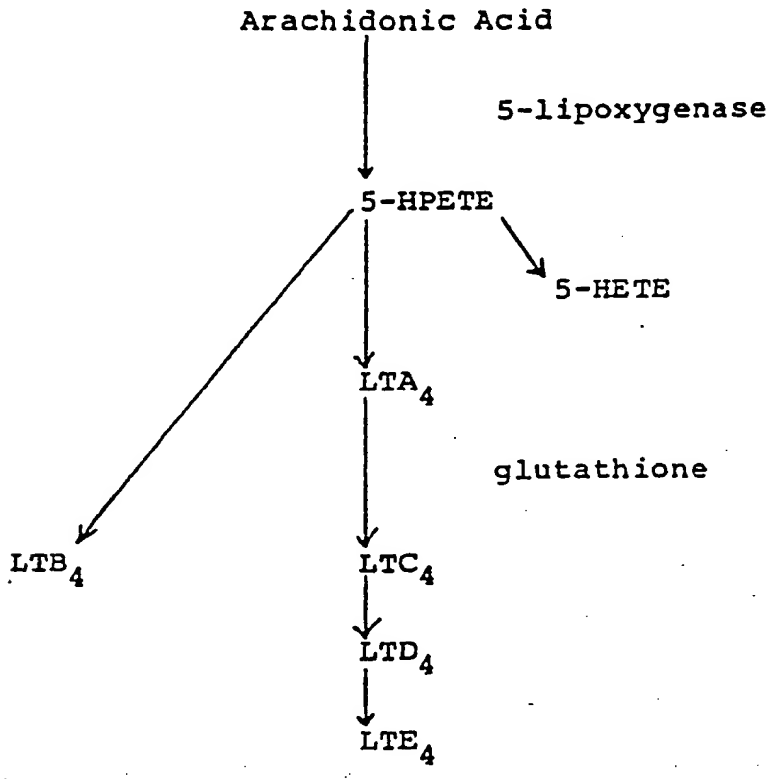
Other Indolent Inflammation

Radiation burns and psoriasis are similar to herpes ulcers and DOX burns in that they are persistent, painful dermal inflammations that have not been very successfully treated by existing medical techniques.

Common Mechanism of Action

The present inventor has discovered that such persistent, apparently unrelated dermal inflammations as herpes ulcers, chemical burns, radiation burns and psoriasis are induced and/or propagated by leukotriene inflammatory mediators. The indolent inflammatory process results when tissue membrane destruction releases arachidonic acid, which in turn produce prostaglandins and leukotrienes as well as other inflammatory components. The leukotrienes (LTs) are mediators of ischemia, arterial constriction, neutrophil exocytosis into the dermis and epidermis, and epithelial destruction.

Leukotrienes are members of the eicosanoid family, and are the major biologically active eicosanoids of the lipoxygenase pathway of arachidonic acid metabolism. This pathway is illustrated schematically below:



Production of the leukotrienes requires the initial interaction of arachidonic acid with a cytosolic enzyme called 5-lipoxygenase. The unstable product of this reaction is a 5-hydroperoxy-6,8,11,14-eicosatetraenoic acid (5-HPETE). The 5-HPETE is subsequently reduced to corresponding 5-hydroxy acid (5-HETE) or it may form a 5,6-epoxide intermediate referred to as leukotriene A_4 (LTA_4). LTA_4 is an unstable intermediate in the formation of the remaining leukotrienes. LTA_4 is the precursor of LTB_4, a potent chemotactic agent, and LTC_4, LTD_4, and LTE_4, which are the slow-reacting substances of anaphylaxis.

LTs are produced by a host of cell types including the pulmonary parenchymal cells, macrophage, mast cells, leukocytes, connective tissue cells, and several types of smooth muscle cells, particularly

vascular smooth muscle cells. When tissue and cellular membranes are destroyed by chemical, or some other foreign irritation, arachidonic acid is released which, in the presence of lipoxygenase, initiates the above cascade to the leukotrienes and other chemical mediators of inflammation.

LTs exert a variety of biological actions that contribute to their role as mediators of ischemia and shock. LTB_4 plays a key role as mediator of inflammation by virtue of its chemotactic and chemokinetic properties on blood cells (e.g. eosinophils, macrophages). LTB_4 also promotes the release of lysosmal hydrolases from these and other cell types accompanied by an enhancement of microvascular permeability.

In contrast to LTB_4, the LTC_4, LTD_4, and LTE_4 are more active as stimulators of smooth muscle contraction. LTC_4 and LTD_4 are long acting substances of inflammation that also produce anaphylactic reactions to toxicity and drugs. LTC_4 is metabolized to LTD_4 and then to LTE_4 and there is a significant loss of biological activity as metabolism progresses. Although LTC_4 and LTD_4 are comparable to each other in activity, they are both much more active than LTE_4 in most biological systems.

LTB_4, LTC_4 and LTD_4 are therefore mediators of inflammation. As long as these agents are produced, for example, by continuous exposure to chemicals or virus-induced epithelial destruction, the above LTs and other inflammatory factors will be produced. The present inventor has established that there are elevated concentrations of tissue leukotrienes A_4 (LTA_4), C_4 (LTC_4) and D_4 (LTD_4) associated with herpes vesicles, anthracycline ulcers, radiation burns, sunburns, and psoriasis.

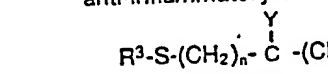
Some dermal inflammations, such as thermal burns, are primarily induced and propagated by prostaglandins. This mechanism occurs when arachadonic acid is released in tissues having enzymes which metabolize the free arachadonic acid to prostaglandins and thromboxanes via the cyclooxygenase pathway. Prostaglandin induced inflammations are less indolent than those induced by leukotrienes and respond to analgesics such as acetyl salicylic acid and other nonsteroidal anti-inflammatory drugs (NSAIDS).

In contrast, tissue damage in herpes ulcers initiated by viruses can induce leukotriene release, with propagation of the inflammation by the continued presence of inflammatory mediators. In DOX induced ulcers, tissue damage results in leukotriene release and is propagated by the continued presence of any DOX and the long acting leukotrienes. Herpes ulcers and DOX ulcers are primarily induced and/or propagated by leukotrienes, as are radiation burns, sunburn and psoriasis.

Many dermal inflammations may be propagated both by leukotrienes and prostaglandins, but one or the other mechanism usually predominates. Inflammations, such as thermal contact burns, which are primarily associated with prostaglandins, are not indolent and their inflammation is substantially reduced by administering acetyl salicyclic acid and/or other NSAIDS. Inflammations primarily induced and/or propagated by leukotrienes, however, are indolent. Inflammations due to leukotrienes may often persist up to many months or even years and are not substantially reduced by salicylic acid and/or NSAIDS. Primarily leukotriene mediated inflammations are often made worse by acetyl salicylic acid and/or the NSAIDS.

SUMMARY OF THE INVENTION

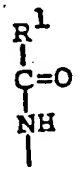
The present invention includes a method and compounds for treating dermal inflammations, such as those which are primarily propagated by leukotrienes. The compounds are also useful in treating prostaglandin propagated inflammations. The inflammations are treated by applying to the inflamed dermis an anti-inflammatory effective amount of the compound



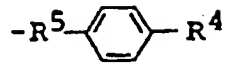
wherein R^3 is H or a thiol; n is 1 to 12; p is 0 to 12; X is a substituted carbonyl, such as an ester or a carboxylic acid; and Y is an aliphatic or branched hydrocarbon, aromatic ring, carbonyl or substituted amide.

Carbonyl X is preferably a carboxylic acid or an ester, such as ethyl ester.

Y is preferably a substituted amide, more preferably

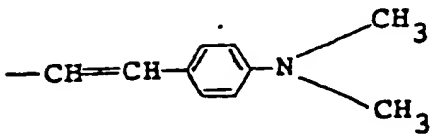


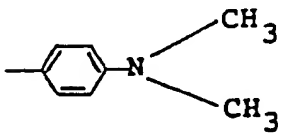
wherein most preferably R^1 is CH_3 or an ultraviolet light absorbing group such as



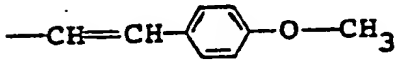
and R^4 or R^5 is an electron donating group, for example substituted or unsubstituted amine at R^4 or alkenyl at R^5.

R^1 is most preferaly





or



n is most preferably 1 to 4, and p is preferably 1 to 4, most preferably 1.

The present invention includes all the foregoing substituents and values for R^1, R^3, R^4, R^5, X, Y, n, and p, both alone and in any combination thereof. Also included are medicinal compositions comprising the compounds and a pharmaceutically inert carrier, such as water or DMSO. The invention also includes the compounds or compositions for use as medicaments for treating inflammations, especially dermal inflammations, such as those which are primarily induced and/or propagated by leukotrienes. Also included is use of any such composition of matter for manufacture of a medicament for therapeutic application.

The compounds and compositions are useful in treating such leukotriene propagated dermal inflammations as herpes simplex and herpes zoster ulcers, doxorubicin burns, radiation burns, and psoriasis. Inflammation in each of these conditions can be substantially reduced and caused to subside by topically dermally applying the compound to the inflammation. In some leukotriene induced inflammations, the compounds interact with peroxides and leukotriene A_4 (LTA_4) to reduce toxic free radicals and interrupt the leukotriene cascade to the highly inflammatory slow releasing substances of anaphylaxis (SRS)-LTC_4 and LTD_4. There is some evidence that the leukotriene cascade is interrupted when the compound forms an adduct with LTA_4. In other instances, the compounds reduce the 5-HEPTE to 5-HETE, which also reduces leukotriene formation.

Prostaglandin type inflammations also have a pathway of production in which a peroxide is an intermediate. The compounds of the present invention can also react with the peroxide intermediate to interfere with prostaglandin production and decrease inflammation.

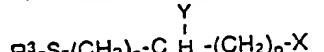
The foregoing and other objects, features, and advantages of the invention will become more apparent from the following detailed description of several preferred embodiments.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The present invention became possible after the inventor determined that some indolent dermal inflammations, such as herpes ulcers, DOX burns, radiation burns and psoriasis, are primarily induced and propagated by leukotriene release in the affected tissue. Inflammation of the ulcer can be reduced or eliminated, however, by topically dermally applying compounds to the inflammation which can form an adduct with LTA_4, which is a highly reactive 5,6-epoxide or reduce the latter to 5-HETE. The LTA_4 adduct

and formation of 5-HETE prevent production of LTB_4, LTD_4 and LTE_4 in the tissue. In the absence of these long acting mediators of inflammation, healing occurs.

The adduct forming compounds are

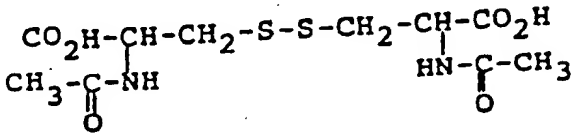


wherein R^3 is H or a thiol; n is 1-12; p is 0-12; X is a substituted carbonyl; and Y is an aliphatic or branched hydrocarbon, aromatic carbonyl, or a sustituted amide.

Some of the compounds of the present invention which form adducts with th LTA_4 epoxide are

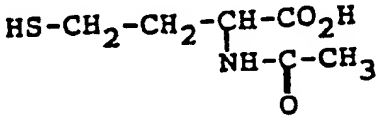
Example 1

N,N'-dicetylcystine (N-DAC):



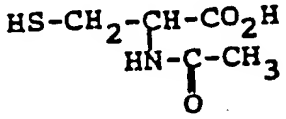
Example 2

N-acetylhomocysteine (NAH) :

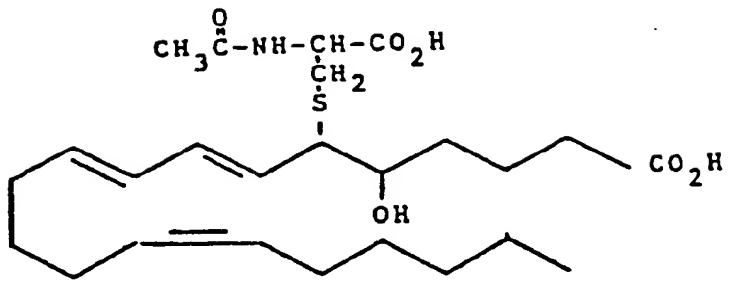


Example 3

N-acetylcysteine (NAC) :



The LTA_4-NAC adduct which is obtained when NAC is topically applied to leukotriene propagated inflammations is shown below.

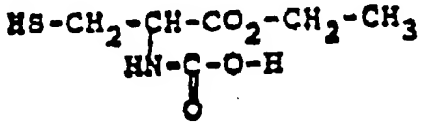


Leukotriene A_4 mercapturate

The thiol group of NAC binds to LTA_4 where indicated above. This is the same position at which the thiol group of each of the compounds of the present invention binds to LTA_4.

Example 4

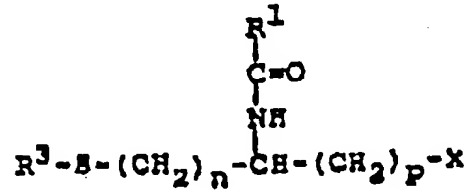
N-acetylcysteine ethyl ester (NACE) :



The compounds in Examples 1-4 are derivatives of the amino acids cysteine and cystine. They are preferably contained in a pharamaceutically inert carrier such as water or DMSO. On a weight basis, 5-20% N-DAC, NAC, NAH, or NACE is preferably mixed with the carrier. Although a 5-20% concentration is preferred, a concentration as high as 100% can be used. A preservative such as EDTA 0.1% may also be included. These agents effectively reduce pain and increase healing of skin vesicles, ulcers, and eruptions from herpes simplex, herpes zoster, DOX burns, radiation burns, and sunburns.

Example 5

Another group of adduct forming compounds are especially useful in treating sunburn. These compounds are



wherein R^3 is H or thiol; n is 1-12; p is 0-12; X is a substituted carbonyl; and R^1 is an ultraviolet light absorbing group such as

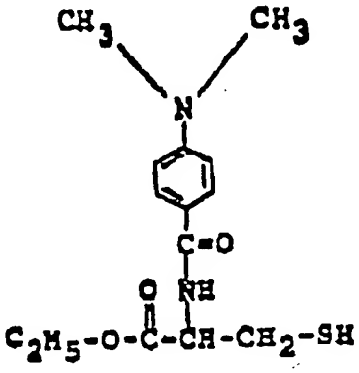
wherein R^4 or R^5 is an electron donating group. For example, R^4 can be a substituted amine or R^5 can be

alkenyl.

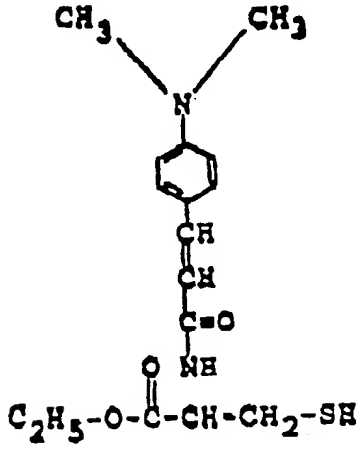
Th ultraviolet light absorbing group helps the compound act as a sunscreen while leukotriene production is also interrupted by formation of the adduct. The compound is preferably placed in an inert carrier such as peanut oil or a fragment oil for application to sunburned skin. Additional sunburn damage is therefore prevented or diminished while healing takes place.

Specific examples of ultraviolet light absorbing compounds are given in subsequent Examples 6-8.

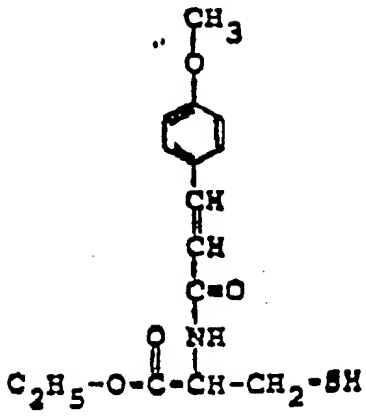
Example 6



Example 7

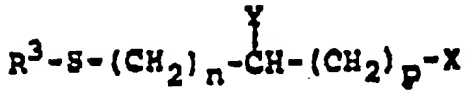


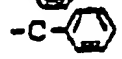
Example 8



Additional examples of compounds within the scope of the invention are given in the following chart:

Examples 9-15



Example No.	X	Y	n	p	R^1	R^3
9	COOH	$NHCOR^1$	3	1	CH_3	H
10	$COOCH_3$	$NHCOR^1$	4	2	CH_3	H
11	$COOCH_3$	$NHCOR^1$	12	4	CH_3	H
12	COOH	C_2H_5	1	12	-	SH
13	COOH	$-C(CH_3)_2$	1	1	-	SH
14	$(CH_2)_2$-COOH		1	1	-	H
15	$(CH_2)_2$-COOH		2	1	-	H

Starting Materials

NAC is commercially available from Aldrich Chemical Company, Milwaukee, Wisconsin in the United States and Europe. It is the acetyl amide of the amino acid cysteine. Its use has predominantly been as a mucolytic agent in the treatment of bronchial congestion and bronchitis. It chemically disrupts disulfide bonds in intra bronchial mucin, thus liquifying bronchial mucous plugs.

NAH was purchased from Fluka Chemical Company of Switzerland. N-Acetylcysteine ethyl ester is also commercially available.

N-DAC was synthesized in the following manner;

1-Cystine (0.05 mole, 12g) was suspended in 50 ml of water and dissolved by adding 8 M potassium hydroxide until the solution was pH 12. At 0° C to 3° C, acetic anhydride (0.15 mole 15.3 g) was added in small portions as the pH of the solution was maintained between 10 and 10.5 with 8 M potassium hydroxide. After the addition of acetic anhydride, the solution was allowed to stand one hour at room temperature at pH 10 and then adjusted to pH 3 with concentrat d hydrochloric acid. The solution was concentrated in vacuo, and the viscous residue extracted three times with 100 ml portions of an acetone-water mixture (93:7 v/v). The acetone extract was concentrated in vacuo and dried in a desiccator over phosphorus pentoxide and sodium hydroxide. The residue was dissolved in ethanol. The precipitate that formed was removed by centrifugation and the remaining solution chromatographed on Silica Gel-G (Woelin). The columns were developed with chloroform: methanol: acetic acid (80:15:10 v/v). The columns were cut at $R_f = 0.4$ and the N-DAC eluted with methanol. The methanol eluent was concentrated in vacuo to dryness over phosphorus pentoxide. The residue was dissolved in ethanol and the disulfide precipitated by adding the ethanolic solution to diethyl ether. The yield was 22%, and the melting point was 273-275. Anal. Calc. for $C_{10}H_{16}N_2S_2O_5$: C, 35.46; H, 5.20; N, 8.27%. Found: C, 35.94; H; 5.24; N, 8.17%.

General Synthesis Scheme for Substituted Cysteine Amides

To make the substituted cysteine amides shown in Examples 6, 7, and 8, the respective carbonyl chloride derived from p-nitrocinnamic (Example 6), p-nitrobenzoic (Example 7), or p-methoxycinnamic (Example 8) acids (1 molar equivalents) were synthesized by refluxing the acids with four (4) times the molar equivalent of fresh thionyl chloride for 4.5 hours. The mixtures were concentrated, and the residues were dissolved in 20 weight volumes of dry pyridine and 10 volumes of dry methylene chloride or benzene. S-Benzylcysteine ethyl ester (3 molar equivalent) in 20 volumes of pyridine was added slowly to the above residue in pyridine. The reactions were maintained at less than 10 degrees centigrade with external cooling for 3 fours, then stirred overnight.

The mixtures were partitioned with methylene chloride and 1 N sodium hydroxide. The organic phrase was washed with water until neutral and dried over sodium sulfate. The organic phrases were then dried under vacuum. The residues were recrystallized from ethanol water.

The nitro groups were reduced with sodium hydrosulfite (1:10 molar ratio nitro compound/sodium hydrosulfite) in stirring, refluxing aqueous acetone with excess 0.1 N sodium hydroxide (10 volumes). The solution was stirred for 30 minutes after the colors changed to yellow. Water was added (greater than 100 volumes) and the organic solvents removed under distillation. The aqueous solutions were neutralized with 10% acetic acid. The precipitates were recrystallized from ethanol.

The amines were methylated by the procedure of R.F. Borch and A.I. Hassid, J. Org. Chem. 37: 1673-1674, 1972.

The protective benzyl groups were removed by stirring the respective S-benzyl derivatives in dry ether or tetrahydrofuran with freshly prepared, very dry Rainey nickel. The stirring continued at room temperature for 12 hours. The catalyst was removed by filtration and the solution evaporated to dryness. The residues were recrystallized from ethanol to yield the respective cysteine amides.

Topical Absorption in Man and Animals

There are no detectable blood levels of NAC, NAH, N-DAC, or NACE following the application of 5-20% concentrations of these agents in water three times a day to patients with open ulcers. In a rabbit animal model that was described previously (Cancer Treat. Rep. 65: 1001, 1981), neither NAC, N-DAC nor NAH could be detected in the animal's circulation after topical application of 20% solution of the above agents to the surfaces of rabbit ears.

Method of Use

The following examples illustrate use of the invention.

Example 16

In accordance with the present invention, wet gauze compresses of 20% N-DAC were applied four times a day to four patients with cutaneous ulcers resulting from herpes infections. In all cases, there was reduction in pain and inflammation within 48-72 hours. All lesions were cultured for baterial contamination, and when needed topical garamycin cream (0.1%) was applied twice daily along with the NAC solutions. All four patients demonstrated complete healing with minimal scarring and did not require additional therapy. Debridement of scar formation was performed as needed to allow the deep penetration of N-DAC.

One of these four cases was a 78 year old male who had herpes zoster ulcers over his left chest wall for seven days. The lesions were becoming worse with more drainage and pain. There were clusters of open ulcers with new vesicles developing each day. He was treated four times a day for thirty (30) minutes each time with wet gauze pads soaked with 20% N-DAC. The lesions became painless in 24 hours and all healed in two weeks. No recurrences were noted.

Example 17

Six additional patients with herpes ulcers received topical applications of 20% NAC in water as soaked gauze pads applied to the lesions four to six times a day. All patients treated with NAC exhibited healing and did not require any additional treatment.

Example 18

Two additional patients were treated with 20% NAH in a manner similar to that described in Example 17, with 100% healing.

One of these two patients was a 56 year old male who developed a herpes simplex genital ulcer on his penis. It was an isolated lesion, extremely painful and draining. He as treated topically with moist gauze pads of 20% N-DAC four times a day and the lesion was painless in 24 hours and healed in 10 days. No recurrence was noted in six months.

Example 19

Four patients were treated who were suffering from cutaneous ulcers produced following accidental extravasation of DOX during intravenous administration of the drug. A 20% N-DAC (in water solution) was applied three times a day in the form of wet gauze compresses which remained in place. Within 48-72 hours in all cases there was a reduction in pain, redness and inflammation. All lesions were cultured for bacterial contamination and where needed topical garamycin cream (0.1%) was applied twice daily along with the N-DAC solutions. All four patients demonstrated complete healing which did not require skin grafting.

Debridement of scar formation was performed as needed to allow the deep penetration of N-DAC. A collagen scar was the result of the above applications of N-DAC

One of these four patients was a 32-year old black female with advanced breast cancer who developed a painful skin ulcer following inadvertent DOX infiltration during her therapy. Accepted methods of treatment (intradermal sodium bicarbonate, dexamethasone, etc.) provided no relief, and she refused surgery. Gauze bandages soaked with N-DAC (20% solution) were applied four times a day over the ulcer. Over a 12-week period the lesion underwent scar formation and healed. After healing, the patient had complete leverage and rotation of the arm and wrist with complete scar formation.

Example 20

Two patients with DOX-induced ulcers received topical applications of 20% NAC in water as continuous gauze soaks to the lesions. Both patients had permanent scar formation not requiring surgery following NAC application.

One of these patients was a 67 year-old white female with advanced breast cancer which had spread to the lung and who was treated with DOX. During her therapy, a significant amount of DOX extravasated into

her forearm. Over a one-month period a large ulcer formed, but she was not a candidate for general surgery to repair the lesion. She was treated with 20% NAC in water topically. The solution was applied three times a day to gauze pads over the lesion for two months. There was immediate reduction in pain and redness followed by continuous scar formation with epithelialization and granulation until a permanent scar resulted that allowed free motion.

The effect of oral NAC on cardiac toxicities has been reported (U.S. Pat. 4,331,648) and shown not to reduce DOX antitumor activity. All six patients in Examples 19 and 20 were continued on chemotherapy—three continued on doxorubicin combinations and three on 5-Fluorourcil, Cyclophosphamide and Methotrexate therapy. No changes in response patterns were seen in the patients.

Example 21

Psoriasis and radiation burns would be treated with N-DAC, NAC, NAH, NACE in the manner described in Examples 16-20.

Example 22

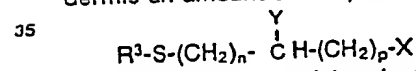
Sunburn could be treated in the manner described in any of Examples 16-20. Alternatively, the compounds in any of Examples 5-8 could be topically applied to sunburned skin to promote healing and prevent additional sunburn damage.

Having illustrated and described the principles of my Invention with reference to several preferred embodiments, it should be apparent to those persons skilled in the art that such invention may be modified in arrangement and detail without departing from such principles. I claim as my invention all such modifications as come within the true spirit and scope of the following claims.

The features disclosed in the foregoing description and in the following claims may, both separately and in any combination thereof, be material for realising the Invention in diverse forms thereof.

Claims

1. A method of treating a dermal inflammation, the method comprising topically applying to an inflamed dermis an amount of compound sufficient to inhibit inflammation, the compound being

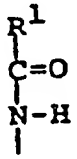


wherein R^3 is H or thiol; n is 1-12; p is 0-12; X is a substituted carbonyl; and Y is aliphatic or branched hydrocarbon, aromatic carbonyl, or substituted amide.

2. The method of claim 1 wherein Y is a substituted amide.

3. The method of claim 2 wherein n is 1-4.

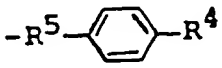
4. The method of claim 1 wherein Y is



and R^1 is CH_3 or an ultraviolet light absorbing group.

5. The method of claim 4 wherein R^1 is an ultraviolet light absorbing aromatic group.

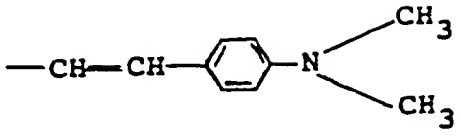
6. The method of claim 4 wherein R^1 is

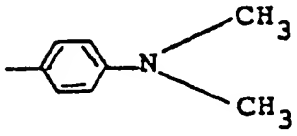


wherein R^4 or R^5 is an electron donating group.

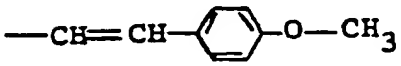
7. The method of claim 6 wherein R^4 is a substituted or unsubstituted amine.

8. The method of claim 6 wherein R^5 is alkenyl.
9. The method of claim 4 wherein R^1 is

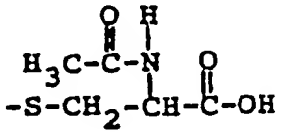




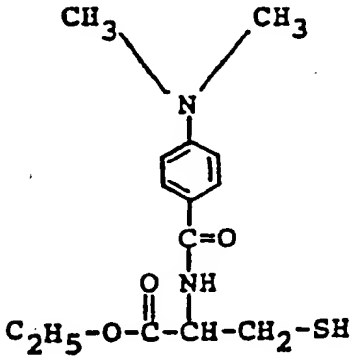
or



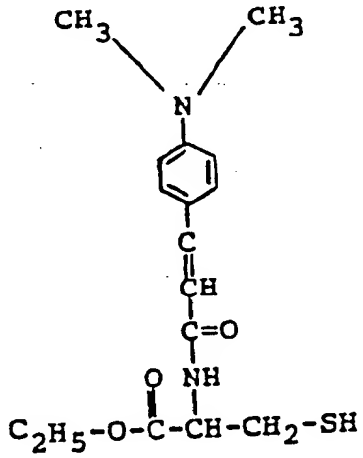
10. The method of claim 1 wherein R^3 is



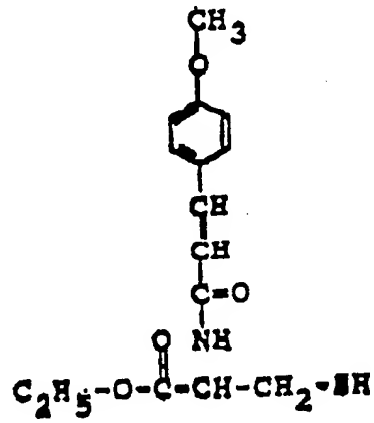
11. The method of claim 1 wherein R^3 is H.
12. The method of claim 1 wherein the compound is N, N'-diacetylcystine.
13. The method of claim 1 wherein the compound is N-acetylhomocysteine.
14. The method of claim 1 wherein the compound is N-acetylcysteine.
15. The method of claim 1 wherein the compound is N-acetylcysteine ethyl ester.
16. The method of claim 1 wherein the compound is



17. The method of claim 1 wherein the compound is



18. The method of claim 1 wherein the compound is



19. The method of claim 1 wherein the dermal inflammation is primarily induced and/or propagated by leukotrienes.

20. The method of claim 1 wherein the dermal inflammation is a radiation burn.

21. The method of claim 1 wherein the dermal inflammation is a herpes ulcer.

22. The method of claim 1 wherein the dermal inflammation is a chemically induced ulcer.

23. The method of claim 1 wherein the dermal inflammation is an ulcer induced by an anthracycline.

24. The method of claim 1 wherein the dermal inflammation is a sunburn.

25. A compound for treating dermal inflammations, comprising

$R^3\text{-}S\text{-}(CH_2)_n\text{-}\underset{\displaystyle Y}{\underset{|}{C}}H\text{-}(CH_2)_p\text{-}X$

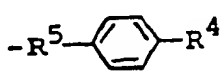
wherein R^3 is H or thiol; n is 1-12; p is 0-12; X is a substituted carbonyl; and Y includes an ultraviolet light absorbing group.

26. The compound of claim 25 wherein Y is

$-NH-\overset{\displaystyle O}{\overset{\|}{C}}-R^1$

R^1 is an ultraviolet light absorbing group, and X is a carboxylic acid or ester.

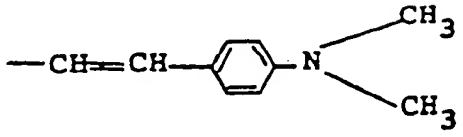
27. The compound of claim 26 wherein R^1 is

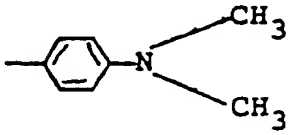


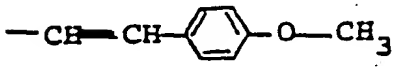
and wherein R^4 or R^5 is an electron donating group.

28. The compound of claim 27 wherein R^4 is a substituted or unsubstituted amine.

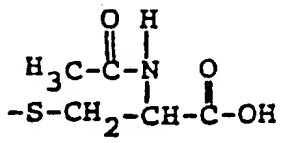
29. The compound of claim 27 wherein R^5 is an alkenyl.
30. The compound of claim 26 wherein R^1 is



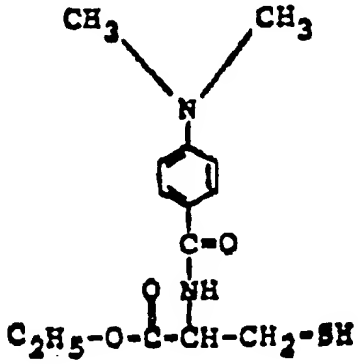




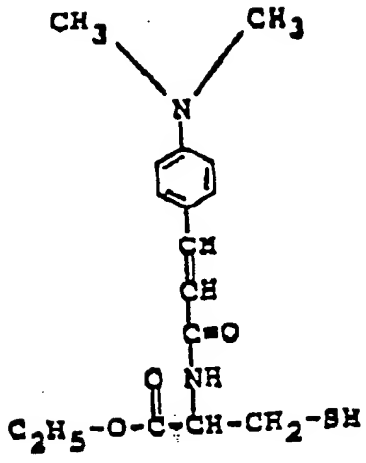
31. The compound of claim 25 wherein R^3 is



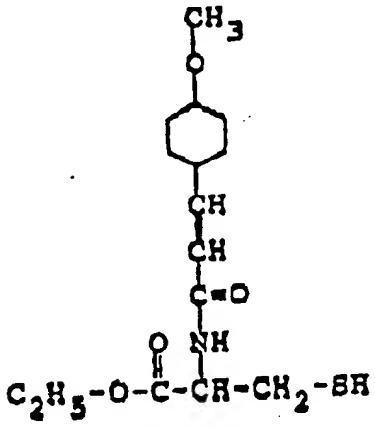
32. The compound of claim 25 wherein the compound is N, N'-diacetylcystine.
33. The compound of claim 25 wherein the compound is N-acetylhomocysteine.
34. The compound of claim 25 wherein the compound is N-acetylcysteine.
35. The compound of claim 25 wherein the compound is N-acetylcysteine ethyl ester.
36. The compound of claim 25 wherein the compound is



37. The compound of claim 25 wherein the compound is



38. The compound of claim 25 wherein the compound is



39. A method of treating dermal inflammations which are primarily induced and/or propagated by leukotrienes, the method comprising topically applying to the inflamed dermis a compound that interferes with leukotriene activity in the inflammation, the compound being applied in an amount sufficient to reduce inflammation.

40. The use of a compound as defined in any one of Claims 1 to 18 in the manufacture of a composition for treating a dermal inflammation.

41. The use according to Claim 40 wherein the dermal inflammation is as defined in any one of Claims 19 to 24.

42. The use according to Claim 40 or 41, wherein the dermal inflammation is induced and propagated by leukotrienes.

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proce dings, as the European search report

Application number
EP 87 30 6353

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
X	EP - A - 0 219 455 (RORY LTD) * Whole document * --	25,34, 40-42	
X	THE JOURNAL OF TRAUMA, vol. 21, no. 8, August 1981, pages 632-644 US; S.M. LEVENSON et al.: "Chemical debridement of burns: mercaptans" * Whole document * --	25,34, 40-42	A 61 K 31/195 A 61 K 7/48
X	US - A - 4 276 284 (BROWN) * Whole document * --	25,34	
X	DE - A - 2 123 380 (ZAMBON SpA) * Whole document * --	25,34	
X	BE - A - 901 885 (BRUSCHETTINI SrL) * Whole document * --	25,34, 40-42	

TECHNICAL FIELDS SEARCHED (Int. Cl.4)

A 61 K

INCOMPLETE SEARCH -2-

The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims.

Claims searched completely: 25-38,40-42

Claims searched incompletely:

Claims not searched: 1-24,39

Reason for the limitation of the search:

Method for treatment of the human or animal body by surgery or therapy (see art. 52(4) of the European Patent Convention).

Place of search	Date of completion of the search	Examiner
THE HAGUE	21-03-1988	FISCHER

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
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DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
X	FR - M - 8205 (MORELLE et al.) * Whole document *	25,32, 40-42	
X	FR - A - 2 092 822 (BRISTOL MYERS) * Whole document *	25,34, 35,40-42	
X	BIOCHEMICAL PHARMACOLOGY, vol. 16, no. 7, 1967, pages 1175-1182 Pergamon Press, Ltd, GB; K.R. BAILEY et al.: "The reduction of experimentally induced inflammation by sulfhydryl compounds" * Whole document *	25,34	TECHNICAL FIELDS SEARCHED (Int. Cl.4)
X	REV.BRAS.MED. vol. 29, no. 4, April 1972, pages 201-205 BR; J. BATISTA VIANA et al.: "Observações preliminares sobre a aplicação da N-acetil-L-cisteína nas úlceras cronicas das pernas" * Page 202, 'conclusões' *	25,34, 40-42	
X	US - A - 3 749 770 (MARTIN) * Whole document *	25,34, 40-42	
E	EP - A - 0 235 064 (ROBERT et al.) * Whole document *	25-30, 38,40-42	